Joint Meeting of the FDA Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee

Assessment of Cardiovascular Safety with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Milton L. Pressler, MD, FACC
Vice President, Clinical Sciences
Pfizer Inc.

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FDA White Oak Campus
Silver Spring, MD

Speakers

Assessment of Cardiovascular Safety with NSAIDs	**Milton L. Pressler, MD, FACC Vice President, Clinical Sciences Pfizer Inc. Groton, CT**
Further Assessment of Current Evidence	**Michael T. Gaffney, PhD Vice President, Statistics Pfizer Inc. New York, NY**
Status of the PRECISION Randomized Clinical Trial (RCT)	**Steven E. Nissen, MD Professor and Chairman, Cardiovascular Medicine Cleveland Clinic, Cleveland, OH**

Pfizer Participants

Safety	**Steven R. Bailey, MD MPH MBA** **Vice President, Worldwide Safety and Regulatory**
Medical	**David E. Kellstein, PhD** **Senior Director, Consumer Healthcare Medical**
Medical	**Peter W. Park, PhD** **Senior Director, Medical Affairs**
Medical	**Jonathan J. Shilstone, PhD** **Senior Director, Medical Affairs**
Epidemiology	**Rachel E. Sobel, DrPH** **Senior Director, Epidemiology**

Agenda

- **Scope of Presentation**
- Background and Methodology
- Cardiovascular Safety with Nonprescription Ibuprofen
- Cardiovascular Safety with Prescription NSAIDs
- Further Assessment of Current Evidence
- Conclusions

Scope of Our Presentation

- Review and analyze the literature published since the 2005 Advisory Committee and draw conclusions on the risk of cardiovascular (CV) events associated with use of NSAIDs
- Address whether these reports and analyses permit differentiation among the NSAID class in terms of CV safety
- Examine whether equipoise remains for the PRECISION study

Pfizer NSAIDs in the United States

	Generic Name	Brand Name	Maximum dose/day	Indications
Prescription	celecoxib	Celebrex®	400 mg	OA, RA, JRA, Ankylosing Spondylitis, Acute Pain, Primary Dysmenorrhea
	diclofenac sodium/ misoprostol	Arthrotec®	150 mg/600 mcg	OA**
			200 mg/800 mcg	RA**
	flurbiprofen	Ansaid®	300 mg	OA, RA
	oxaprozin	Daypro®	1200 mg	OA, RA, JRA
	oxaprozin potassium	Daypro Alta™	1200 mg	OA, RA
	piroxicam	Feldene®	20 mg	OA, RA
Nonprescription	ibuprofen	Advil®	1200 mg	temporarily relieves minor aches and pains*

*Up to 10 days due to: headache, toothache, backache, menstrual cramps, the common cold, muscular aches, minor pain of arthritis and temporarily reduces fever; **in patients at high risk of developing NSAID-induced gastric and duodenal ulcers and their complications
JRA, juvenile rheumatoid arthritis; OA, osteoarthritis; RA, rheumatoid arthritis

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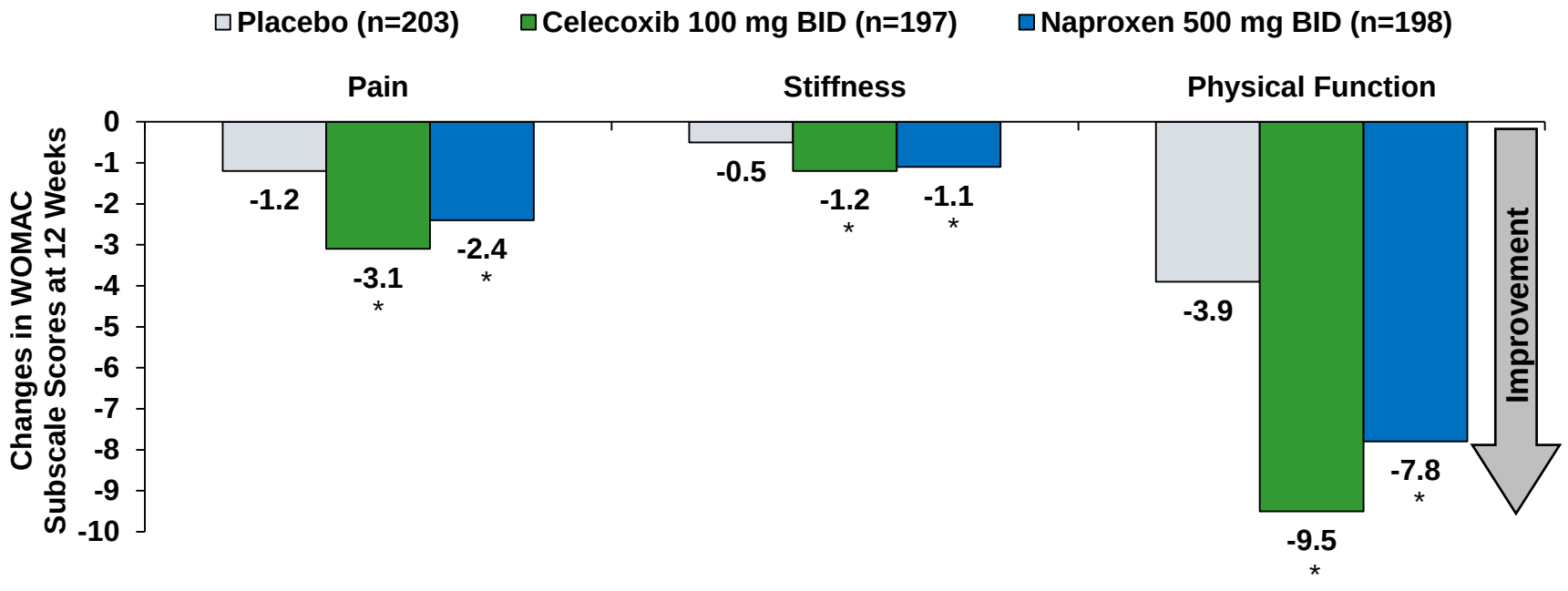
Medical Need for NSAIDs in the US

- 50 million adults have doctor-diagnosed arthritis[1]
- Arthritic conditions are among the most common causes of disability among US adults[2]
- 29 million adults are regular users of NSAIDs[3]

[1]CDC. MMWR 2010;59:1261-1265
[2]CDC. MMWR 2005;58:421-426
[3]Zhou Y et al. Pharmacoepidemiol Drug Saf 2013; DOI: 10.1002/pds.3463

Knee Osteoarthritis: Efficacy in Improving WOMAC Scores

Celecoxib and naproxen both improved WOMAC scores for pain, stiffness, physical function at 12 weeks vs. placebo



*Statistically significant vs. placebo (p<0.05)
BID, twice daily; WOMAC, Western Ontario and McMaster Universities Arthritis Index
Bensen WG et al. Mayo Clin Proc 1999;74:1095-1105; Zhao SZ et al. Pharmacotherapy 1999;19:1269-1278

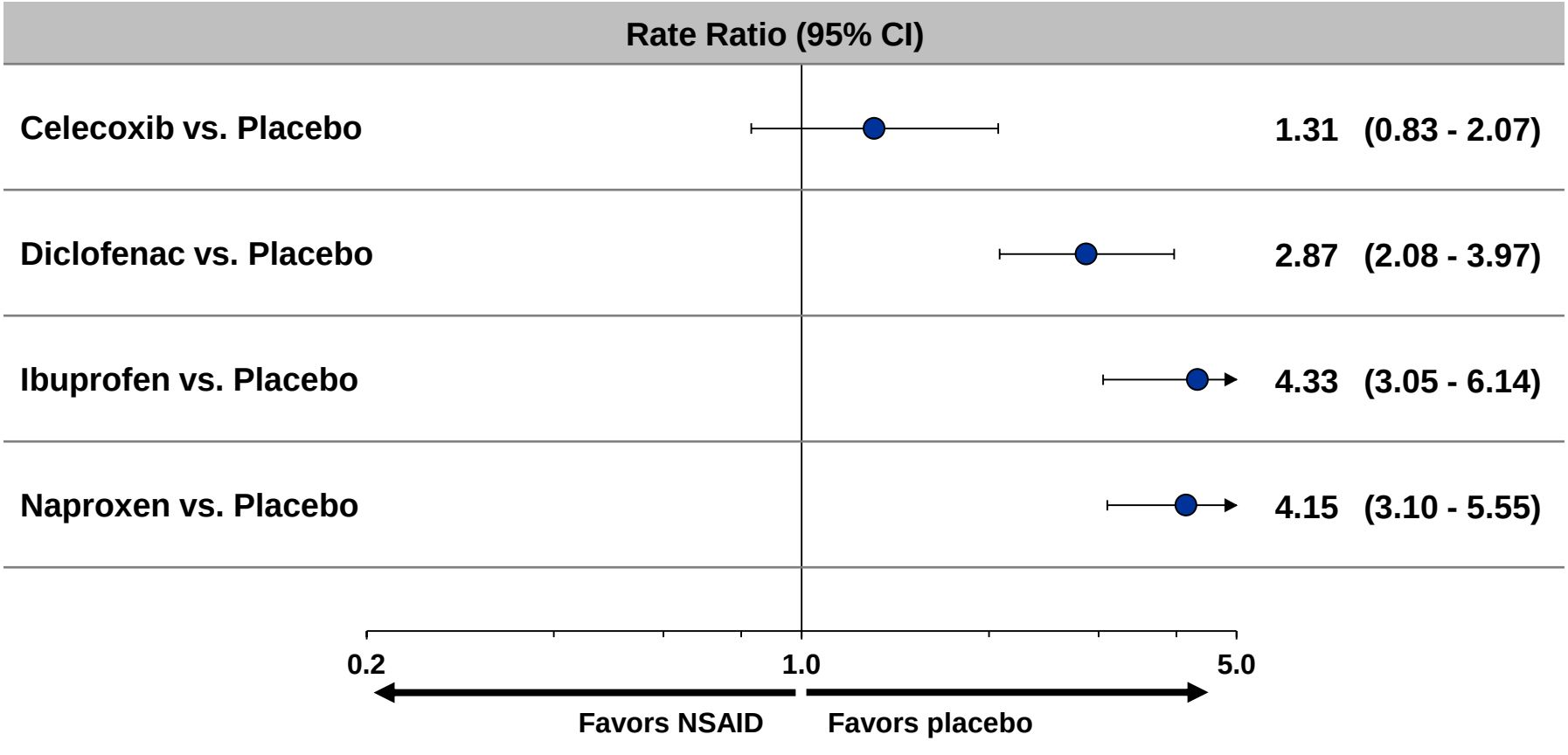
Congestive Heart Failure (CHF) Analyses for NSAIDs

- CHF is a long-recognized risk with prescription NSAIDs[1]
- All NSAIDs have potential to worsen CHF as is well known to practitioners
  - Patients with pre-existing CHF have a higher risk[1]
- The current warning in the US label for congestive heart failure and edema remains appropriate: "…should be used with caution in patients with fluid retention or heart failure"[2]

[1]Mamdani M Lancet 2004;363:1751-1756
[2]CELEBREX [US package insert]. New York, NY: Pfizer; 2013

Symptomatic Upper Gastrointestinal (GI) Events

CNT: Meta-Analysis of Randomized Controlled Trials



CI, confidence interval; Coxib and traditional NSAID Trialists' Collaboration
Bhala N et al. Lancet 2013;382:769-779 and supplement

Review of Available Data

- Systematic literature review: RCTs and observational studies
  - Published December 2004 - November 2013 for Pfizer prescription NSAIDs
  - Published since 1965 for nonprescription ibuprofen
  - www.clinicaltrials.gov and ENCePP for unpublished results
  - 113 articles cited in FDA's reference list
- Systematic review of Pfizer clinical trials
  - 89 celecoxib study meta-analysis of RCTs
  - 8 nonprescription ibuprofen trials
  - Data on CV events were examined for diclofenac-misoprostol, flurbiprofen, oxaprozin, oxaprozin potassium, and piroxicam but will not be presented

ENCePP, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; RCT, randomized controlled trial

Cardiovascular Event Endpoints

- Major Adverse Cardiac Events (MACE)
  - MACE defined as myocardial infarction, stroke, and cardiovascular death
  - Analysis of individual components of MACE (MI/stroke/CV death) considered
    - Fewer events and less power
    - Competing risks
    - Composite is more conservative in capturing events of interest

MI, Myocardial Infarction

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- Cardiovascular Safety with Prescription NSAIDs
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Nonprescription Ibuprofen for Short Term Use at Lower Doses

- First non-aspirin NSAID approved for nonprescription use in the US in 1984
- Labeled indication
  - *Temporarily relieves minor aches and pains due to: headache, toothache, backache, menstrual cramps, the common cold, muscular aches, minor pain of arthritis*
  - *Temporarily reduces fever*
  - *Treats migraine (in specially labeled packaging)*
- The most widely used nonprescription NSAID in the US[1]
- Maximum labeled nonprescription dose and duration is 1200 mg/day for up to 10 days

[1]Information Resources Incorporated (IRI), 52 weeks ending 01/12/14

Cardiovascular Events

Meta-Analyses of Observational Studies of Low-Dose Ibuprofen (≤1800 mg/day)

- McGettigan and Henry 2011: Meta-analysis of 11 observational studies[1]
  - Endpoint: Risk of various CV events for users vs. non-users/remote users
  - Results: Low-dose ibuprofen risk ratio = 1.05 (0.96 - 1.15)
- Varas-Lorenzo et al. 2013: Meta-analysis of 7 observational studies[2]
  - Endpoint: MI risk among users vs. non-users or remote users
  - Results: Low-dose ibuprofen risk ratio = 0.97 (0.76 - 1.22)

[1]McGettigan P, Henry D PLoS Med 2011;8:e1001098
[2]Varas-Lorenzo C. et al. Pharmacoepidemiol Drug Safety 2013;22:559-570

Conclusions: Little Evidence of Increased Risk for Cardiovascular Events with Nonprescription Ibuprofen

- Based on the totality of data available as of December 2013 there is little evidence of an increased risk for various CV events with nonprescription ibuprofen
- Current nonprescription ibuprofen packages contain the following warning
  - *"The risk of heart attack or stroke may increase if you use more than directed or for longer than directed"*[1]
- Pfizer concludes the label for nonprescription ibuprofen remains appropriate

[1]Advil® United States Product Label, February 2014

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Studies of Emphasis

- *CNT: Meta-analysis of randomized controlled trials*[1]
  - Vascular and upper GI effects of NSAIDs: Meta-analyses of individual participant data from randomized trials by the Coxib and traditional NSAID Trialists' Collaboration
- *McGettigan and Henry: Meta-analysis of observational studies*[2]
  - Cardiovascular Risk with NSAIDs: Systematic Review of Population-Based Controlled Observational Studies
- *ADAPT: Randomized controlled trial*[3]
  - Alzheimer's Disease Anti-Inflammatory Prevention Trial

[1]Bhala N et al. Lancet 2013;382:769-779
[2]McGettigan P, Henry D PLoS Med 2011;8:e1001098
[3]Martin BK et al. PLoS Clin Trials 2006;1:e33

Study Methods
CNT: Meta-Analysis of Randomized Controlled Trials

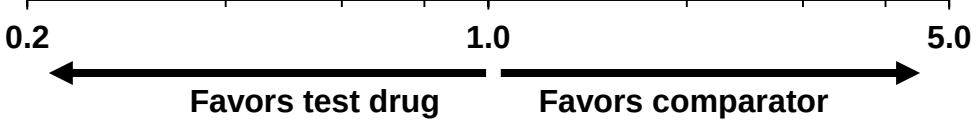
- 280 trials of NSAIDs vs. placebo (124,513 participants, 68,342 person-years)
- 474 trials of one NSAID vs. another NSAID (229,296 participants, 165,456 person-years)
- Pfizer celecoxib clinical trial data was provided to CNT investigators for inclusion
- Primary Endpoints: MACE and upper GI complications
- Combined direct and indirect comparisons
  - COX-2 selective NSAID results by direct comparisons
  - Ibuprofen, diclofenac and naproxen vs. placebo results predominantly by indirect comparisons
- COX-2 selective NSAIDs were assessed as a group for most comparisons

COX, cyclooxygenase
Bhala N et al. Lancet 2013;382:769-779

MACE Events

CNT: Meta-Analysis of Randomized Controlled Trials

Parameters	Rate Ratio (95% CI)	
Individual NSAID comparisons		
Celecoxib[a] vs. Placebo	1.36	(1.00 - 1.84)
Diclofenac vs. Placebo	1.41	(1.12 - 1.78)
Ibuprofen vs. Placebo	1.44	(0.89 - 2.33)
Naproxen vs. Placebo	0.93	(0.69 - 1.27)
Celecoxib comparison		
Celecoxib[a] vs. Diclofenac[b]	0.94	(0.54 - 1.63)
Celecoxib[a] vs. Ibuprofen[b]	1.01	(0.48 - 2.13)
Celecoxib[a] vs. Naproxen[b]	0.93	(0.46 - 1.88)

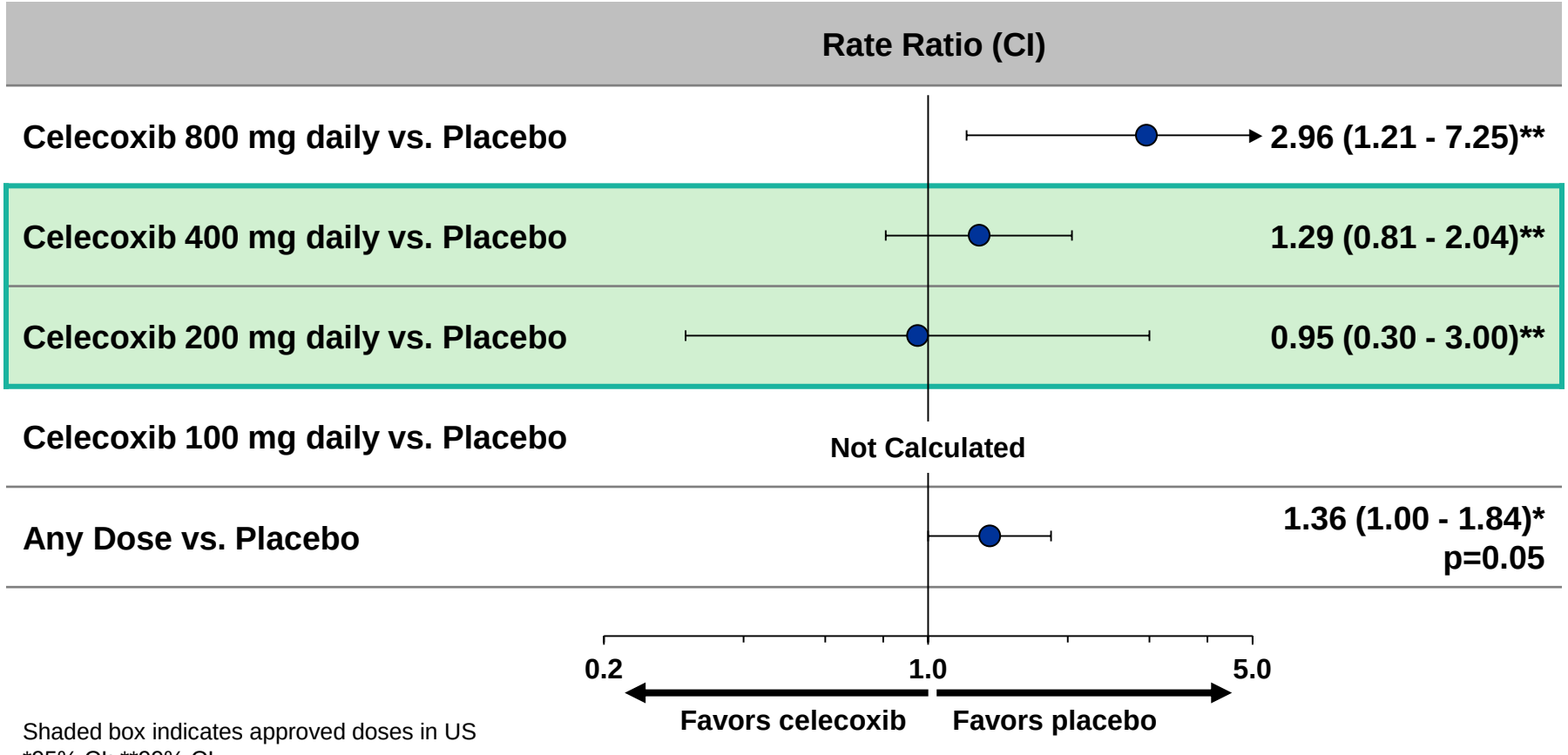


Bhala N et al. Lancet 2013;382:769-779 and Supplement

Note: MACE includes major vascular events; [a]Any dose; [b]Any dose included, but almost all doses were maximum prescription: diclofenac 150 mg daily (“rarely 100 mg”); ibuprofen 2400 mg daily; and naproxen 1000 mg daily (“rarely 440 mg”)

MACE Events: Celecoxib Dose Results

CNT: Meta-Analysis of Randomized Controlled Trials



Shaded box indicates approved doses in US
*95% CI; **99% CI
Bhala N et al. Lancet 2013;382:769-779 and Supplement

Study Methods
ADAPT: Randomized Controlled Trial

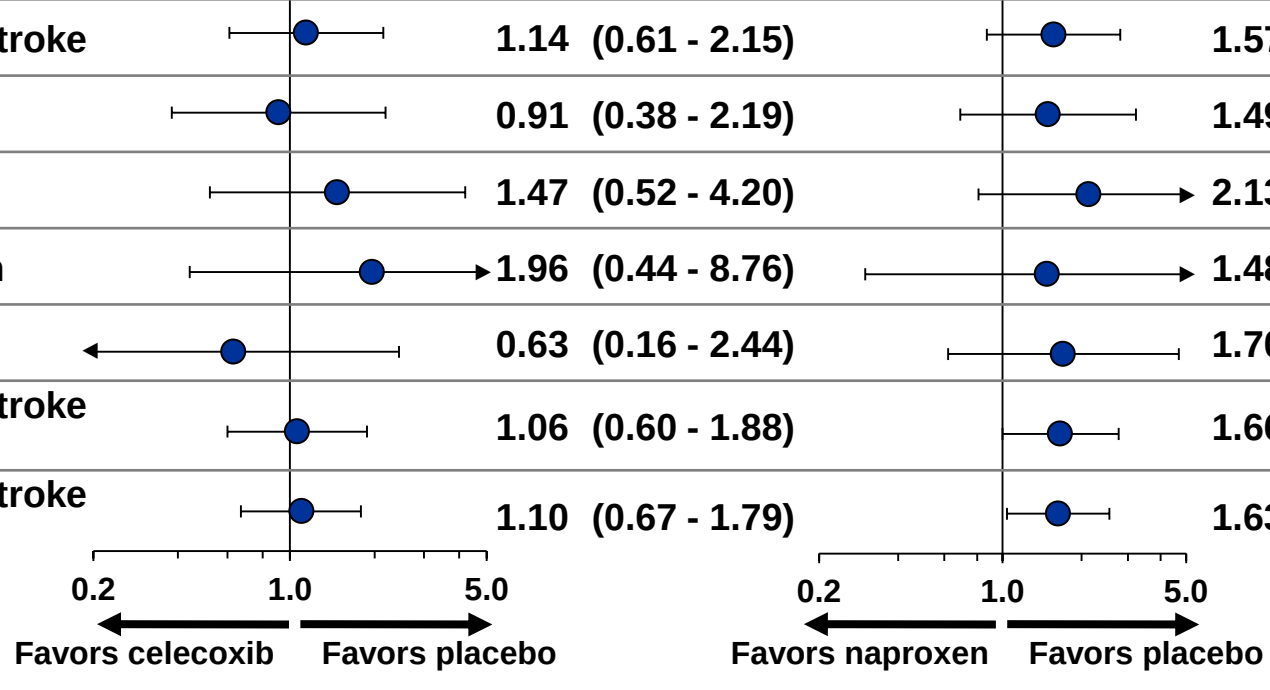
- Alzheimer's disease prevention trial
  - 2528 subjects randomized 2:2:3 to either celecoxib 200 mg BID, naproxen sodium 220 mg BID, or placebo. Median treatment duration ~15 months, and median follow-up ~23 months
  - Primary outcome was the incidence of Alzheimer's disease
- ADAPT was suspended when an excess of MACE was found in the combined celecoxib arms of the Adenoma Prevention with Celecoxib (APC) trial[1]
- Relative to other trials, ADAPT is noteworthy because
  - Direct comparison of celecoxib vs. placebo, and naproxen vs. placebo
  - Nonprescription dose of naproxen 220 mg BID
  - Older population, more males, more aspirin use
- CV Endpoint: Various CV events (not adjudicated) and composites including MACE
- CV analysis was not pre-specified

[1]Solomon S et al. NEJM 2005;352:1071-1080
Martin BK et al. PLoS Clin Trials 2006;1:e33

Cardiovascular Events

ADAPT: Randomized Controlled Trial

Parameters	Celecoxib vs. Placebo Risk Ratio (95% CI)	Naproxen vs. Placebo Risk Ratio (95% CI)
CV Death/MI/Stroke	1.14 (0.61 - 2.15)	1.57 (0.87 - 2.81)
MI	0.91 (0.38 - 2.19)	1.49 (0.69 - 3.22)
Stroke	1.47 (0.52 - 4.20)	2.13 (0.81 - 5.60)
CV Death	1.96 (0.44 - 8.76)	1.48 (0.30 - 7.32)
CHF	0.63 (0.16 - 2.44)	1.70 (0.62 - 4.69)
CV Death/MI/Stroke + CHF	1.06 (0.60 - 1.88)	1.66 (1.00 - 2.77)
CV Death/MI/Stroke + CHF + TIA	1.10 (0.67 - 1.79)	1.63 (1.04 - 2.55)



TIA, transient ischemic attack

Martin BK et al. PLoS Clin Trials 2006;1:e33

Study Methods

McGettigan and Henry Meta-Analysis of Observational Studies

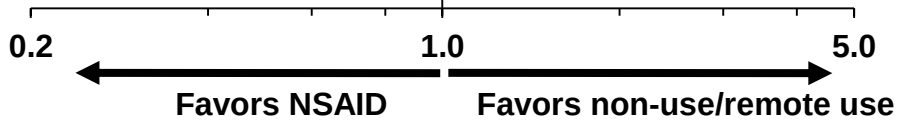
- Meta-analysis of 51 observational studies
  - 30 case-control: 184,946 cases, 1.2M controls
  - 21 cohort: 2.7M NSAID users; 2.4M non-users
- Endpoint: Composite CV endpoint
  - 29 studies examined MI; 8 stroke; 13 non-MACE composite; 6 CV death; 3 any death
- Populations primarily from Europe and the US and were on average over 65 years old

McGettigan P, Henry D PLoS Med 2011;8:e1001098 and Supplement

Cardiovascular Events

McGettigan and Henry Meta-Analysis of Observational Studies

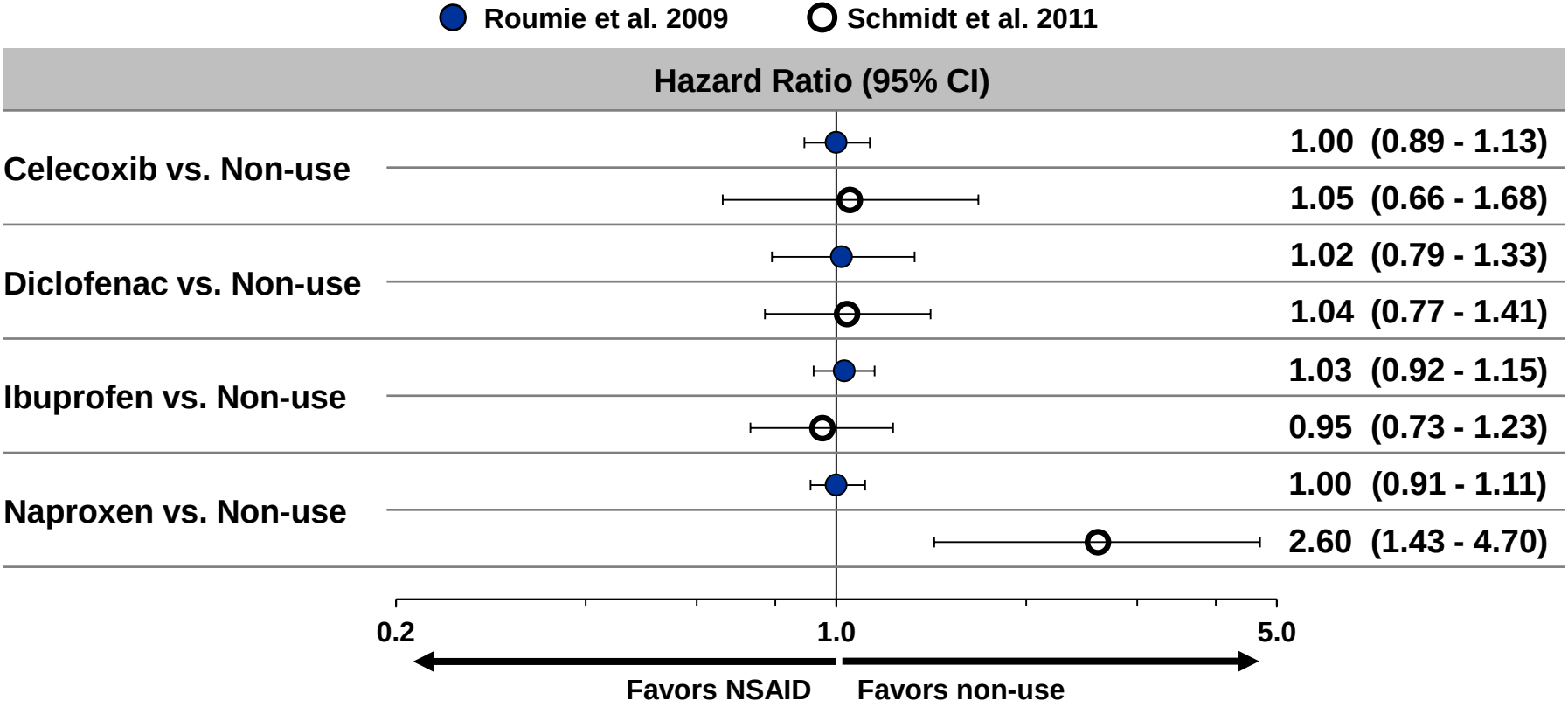
Drug vs. Non-use/Remote use	Total Number of Studies	Pooled Risk Ratio (95% CI)	
Naproxen	41	1.09	(1.02 - 1.16)
Ibuprofen	38	1.18	(1.11 - 1.25)
Celecoxib	35	1.17	(1.08 - 1.27)
Rofecoxib	34	1.45	(1.33 - 1.59)
Diclofenac	29	1.40	(1.27 - 1.55)
Indomethacin	14	1.30	(1.19 - 1.41)
Piroxicam	8	1.08	(0.91 - 1.30)
Meloxicam	7	1.20	(1.07 - 1.33)
Etodolac	5	1.55	(1.28 - 1.87)
Etoricoxib	4	2.05	(1.45 - 2.88)
Valdecoxib	5	1.05	(0.81 - 1.36)



McGettigan P, Henry D PLoS Med 2011;8:e1001098

MACE Events

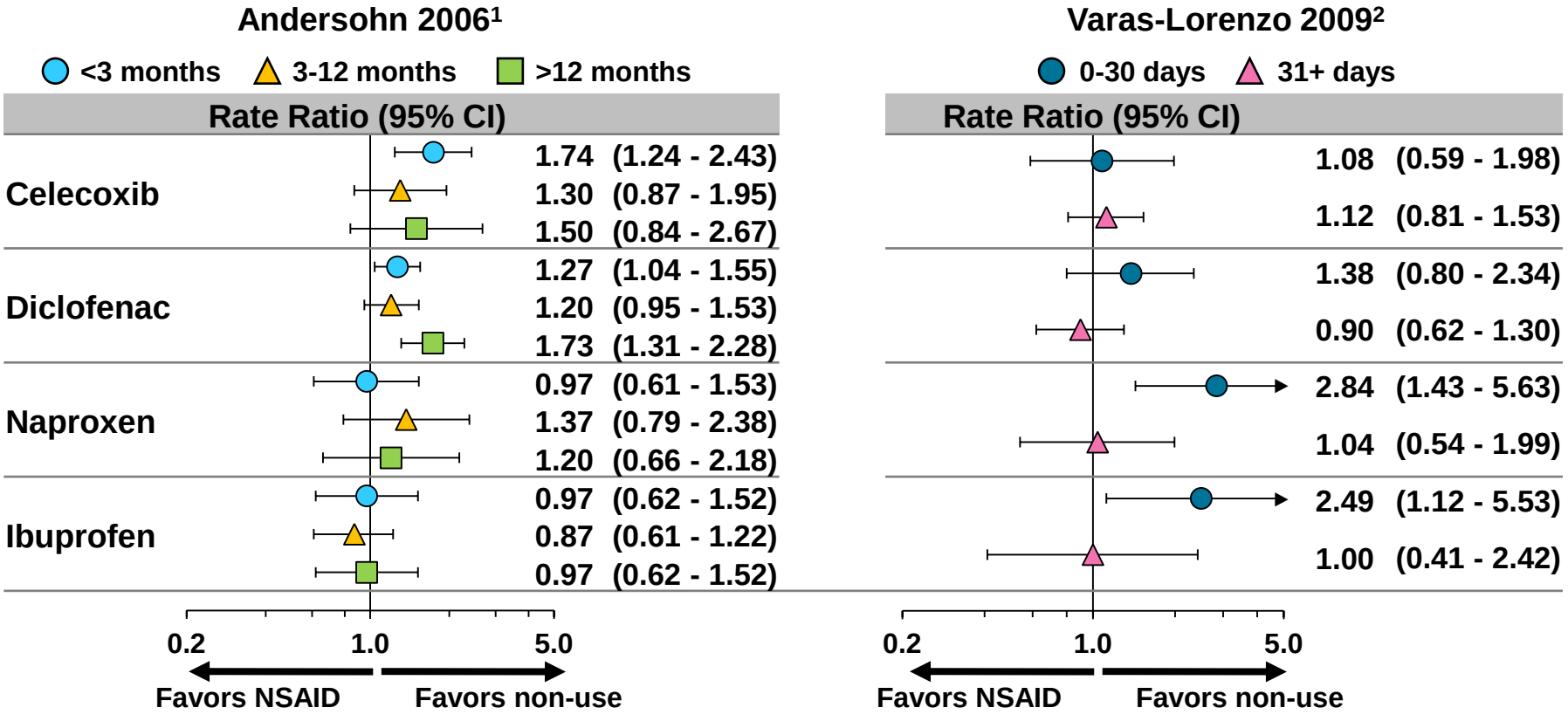
Individual Observational Studies



Roumie CL et al. Pharmacoepidemiol Drug Saf 2009;18:1053-1063; Schmidt M et al. Pharmacotherapy 2011;31:458-468

Latency Period for Increased Risk of MI

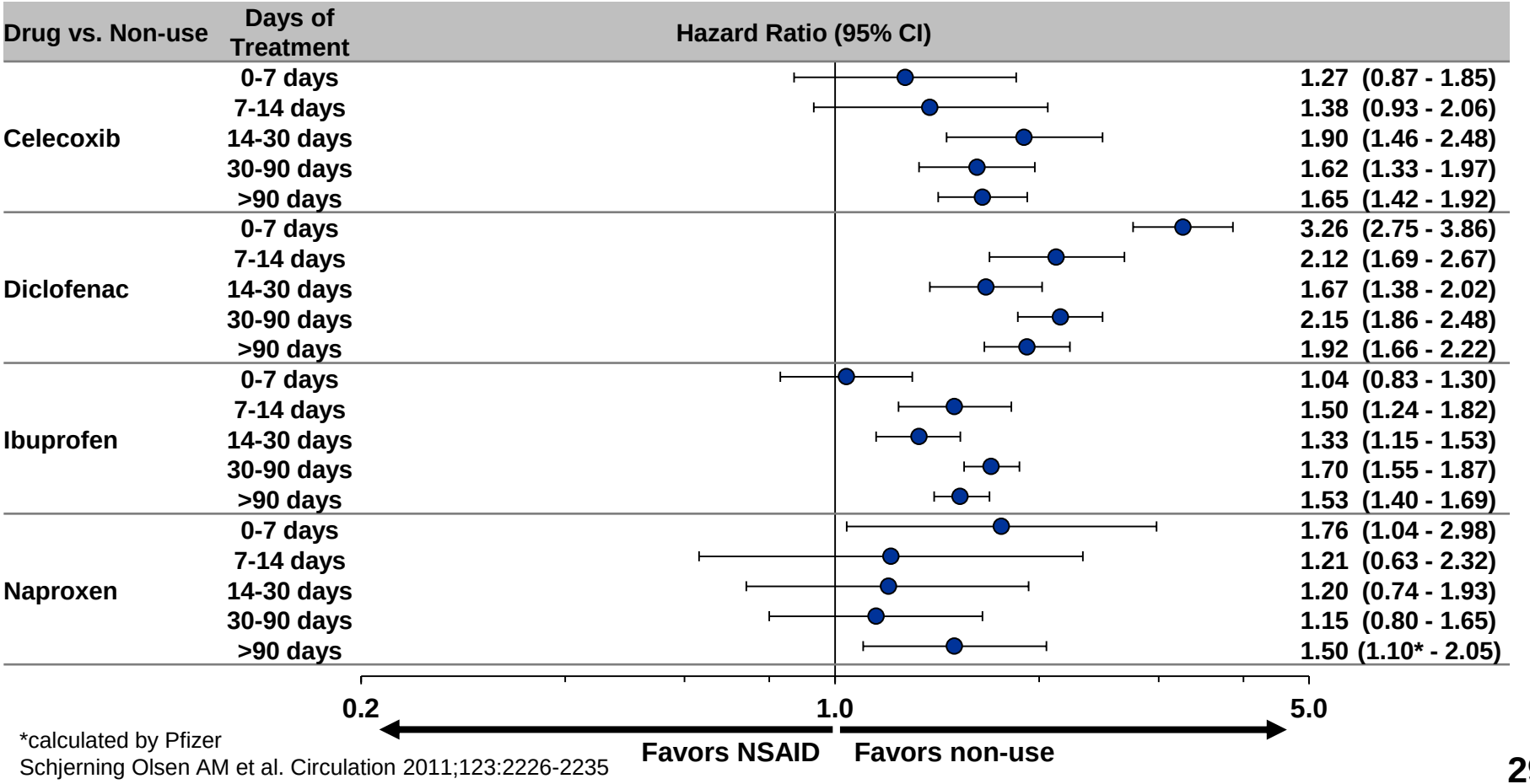
Observational Studies



[1]Andersohn F et al. Circulation 2006;37:1725-1730; [2]Varas-Lorenzo C et al. Pharmacoepidemiol Drug Saf 2009;18:1016-1025

Death/Recurrent MI Associated with NSAID Treatment

Danish National Patient Registry, Schjerning Olsen et al. 2011

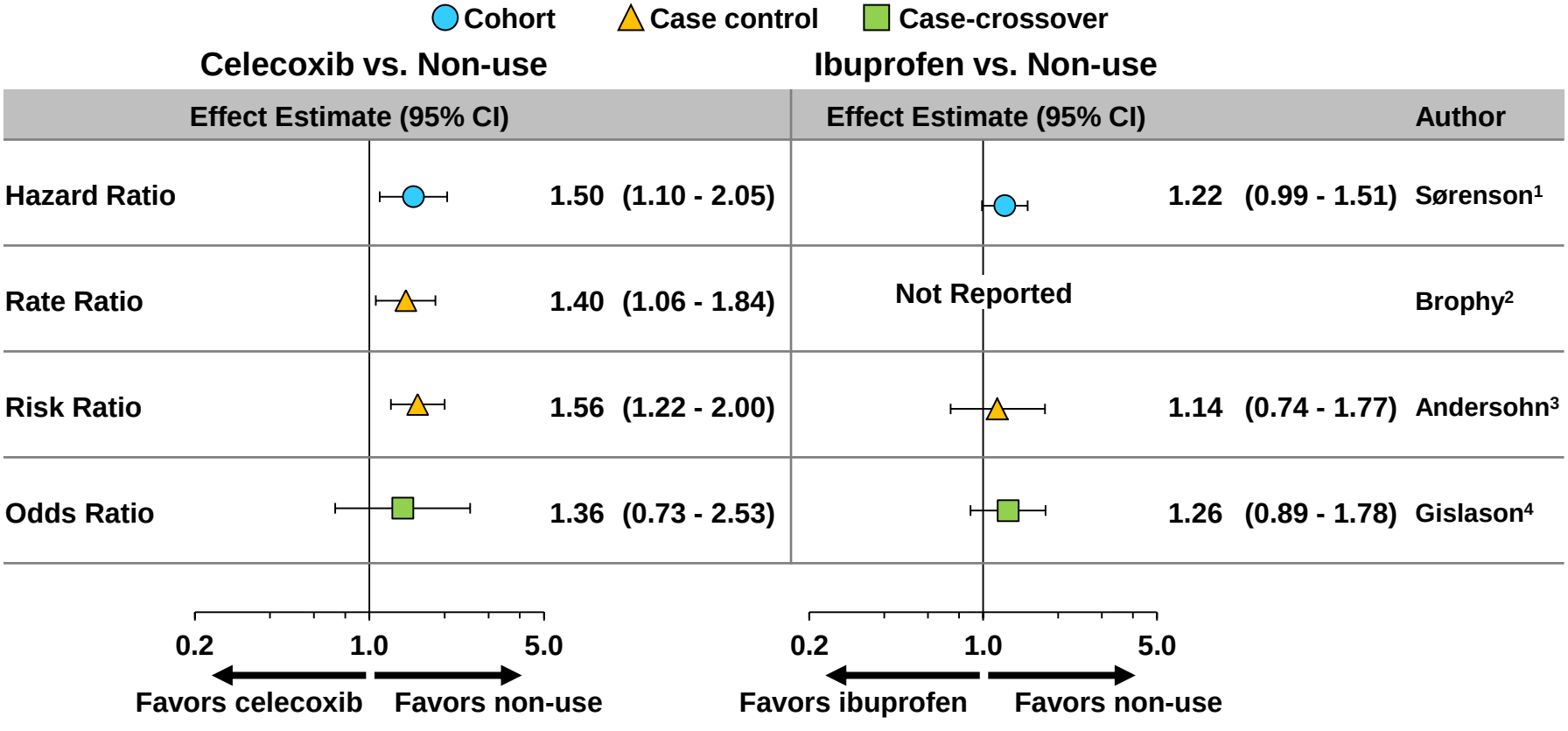


*calculated by Pfizer

Schjerning Olsen AM et al. Circulation 2011;123:2226-2235

Risk of MI in a Post-MI Population

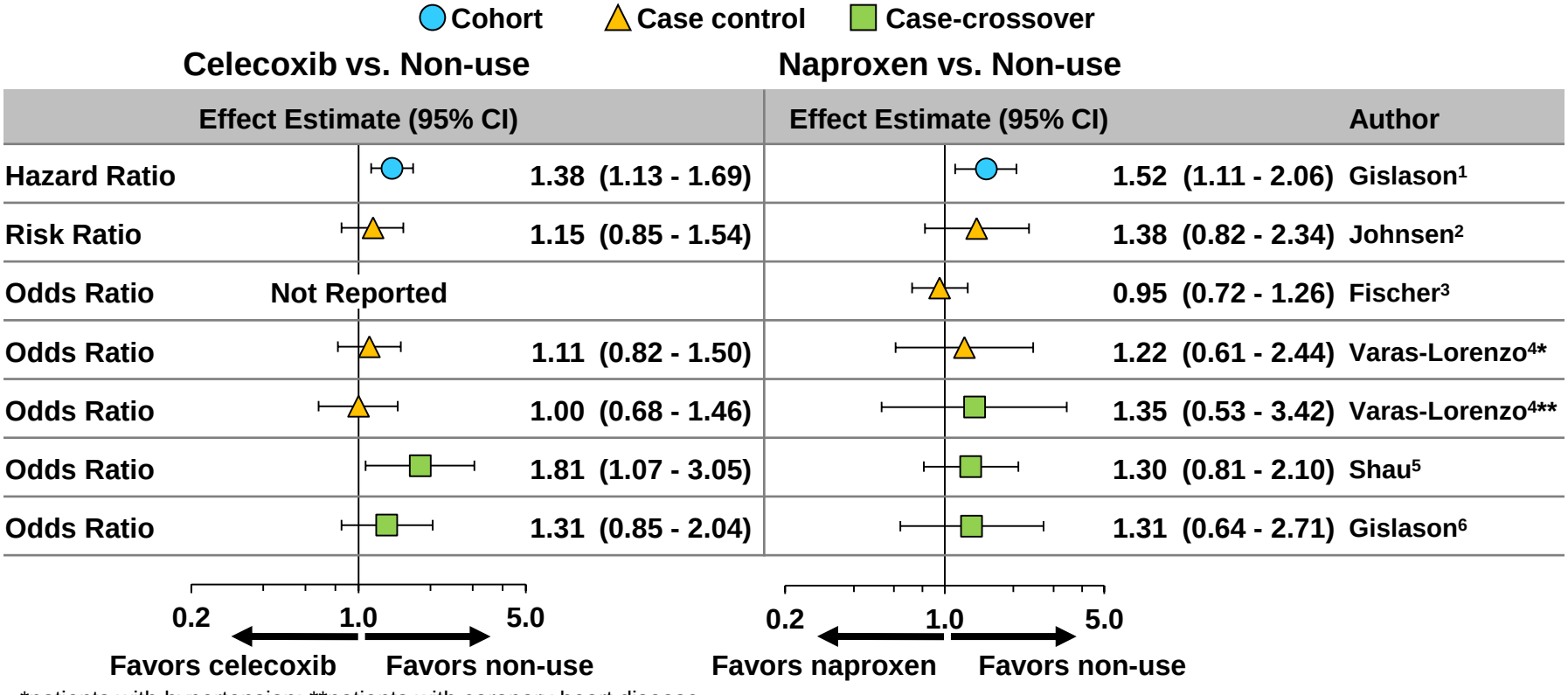
Individual Observational Studies



[1]Sørensen R et al. J Cardiovas Nurs 2008;23:14-19; [2]Brophy JM et al. Heart 2007;93:189-194; [3]Andersohn F et al. Circulation 2006;113:1950-1957; [4]Gislason G et al. Circulation 2006;113:2906-2913

Risk of MI in a High Baseline CV Risk (Non-MI) Population

Individual Observational Studies



*patients with hypertension; **patients with coronary heart disease

[1]Gislason G et al. Arch Intern Med 2009;169:141-149; [2]Johnsen S et al. Arch Intern Med 2005;165:978-984; [3]Fischer LM et al. Pharmacotherapy 2005;25:503-510; [4]Varas-Lorenzo C et al. Pharmacoepidemiol Drug Saf 2009;18:1016-1025; [5]Shau WY et al. BMC Cardiovascular Disorders 2012;12:1471-2261; [6]Gislason G et al. Arch Intern Med 2009;169:141-149

MACE: Conclusions for Prescription NSAIDs

- The evidence continues to show NSAIDs may cause an increased risk of MACE. The effect estimates vs. placebo/non-use generally fall within the 1.00 - 1.50 range for all in the class
  - Outliers for individual NSAIDs exist but are not consistent
  - Cardiovascular risk with naproxen cannot be excluded
  - Insufficient data to determine if there is or is not a latency period
  - Effect estimates for high baseline CV risk or post MI are similar
- The data are consistent with current labeling
- The evidentiary standard for major differentiation among products should be based on robust and compelling data

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MACE Events at Any Dose

CNT: Meta-Analysis of Randomized Controlled Trials

Drug	No.	Events (per 100 patient-years)		Rate Ratio (95% CI)	Weight
		Allocated Coxib	Allocated Placebo		
Celecoxib	41	126 (1.13)	66 (0.74)	1.36 (1.00 - 1.84)	40.7%
Etoricoxib	8	7 (1.52)	4 (1.51)	-	-
Lumiracoxib	9	15 (1.01)	7 (1.05)	-	-
Rofecoxib	25	144 (1.22)	103 (0.89)	1.38 (1.07 - 1.78)	54.9%
Valdecoxib	7	10 (1.62)	3 (1.24)	-	-
GW403681	4	5 (0.77)	0.00	-	-
All Coxibs	86	307 (1.15)	175 (0.82)	1.37 (1.14 - 1.66)	-
		Allocated Coxib	Allocated Naproxen		
Celecoxib	8	23 (0.75)	17 (0.69)	0.93 (0.46 - 1.88)	13.8%
Etoricoxib	11	27 (1.19)	7 (0.44)	2.45 (1.15 - 5.21)	12.0%
Lumiracoxib	6	49 (1.05)	29 (0.67)	1.51 (0.94 - 2.43)	30.3%
Rofecoxib	12	68 (1.18)	35 (0.74)	1.65 (1.09 - 2.49)	40.0%
All Coxibs	34	175	93	1.49 (1.16 - 1.92)	-

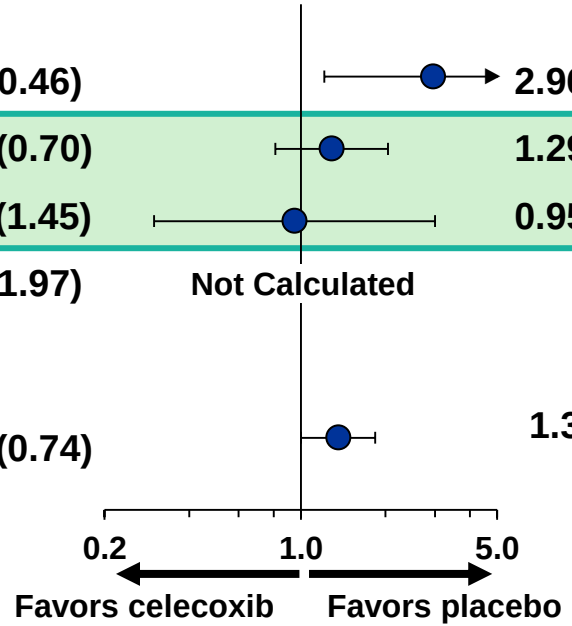
No. is number of comparisons with at least one event

Bhala N et al. Lancet 2013;382:769-779

MACE Events: Celecoxib Dose Results

CNT: Meta-Analysis of Randomized Controlled Trials

Dose	No.	Mean FU (Weeks)	Events (per 100 patient-years) Allocated Coxib	Allocated Placebo	Rate Ratio (CI)
Celecoxib	x^2_1 trend = 6.4 (p=0.0117)				
800 mg Daily	5	83	30 (1.65)	8 (0.46)	2.96 (1.21 - 7.25)**
400 mg Daily	22	74	81 (1.01)	56 (0.70)	1.29 (0.81 - 2.04)**
200 mg Daily	17	10	14 (1.26)	11 (1.45)	0.95 (0.30 - 3.00)**
100 mg Daily	2	8	1 (1.63)	1 (1.97)	Not Calculated
Any Dose	41	n/a	126 (1.13)	66 (0.74)	1.36 (1.00 - 1.84)* p=0.05



Shaded box indicates approved doses in US
No. is number of comparisons with at least one event
*95% CI; **99% CI; FU, follow-up
Bhala N et al. Lancet 2013;382:769-779 and Supplement

Cardiovascular Events

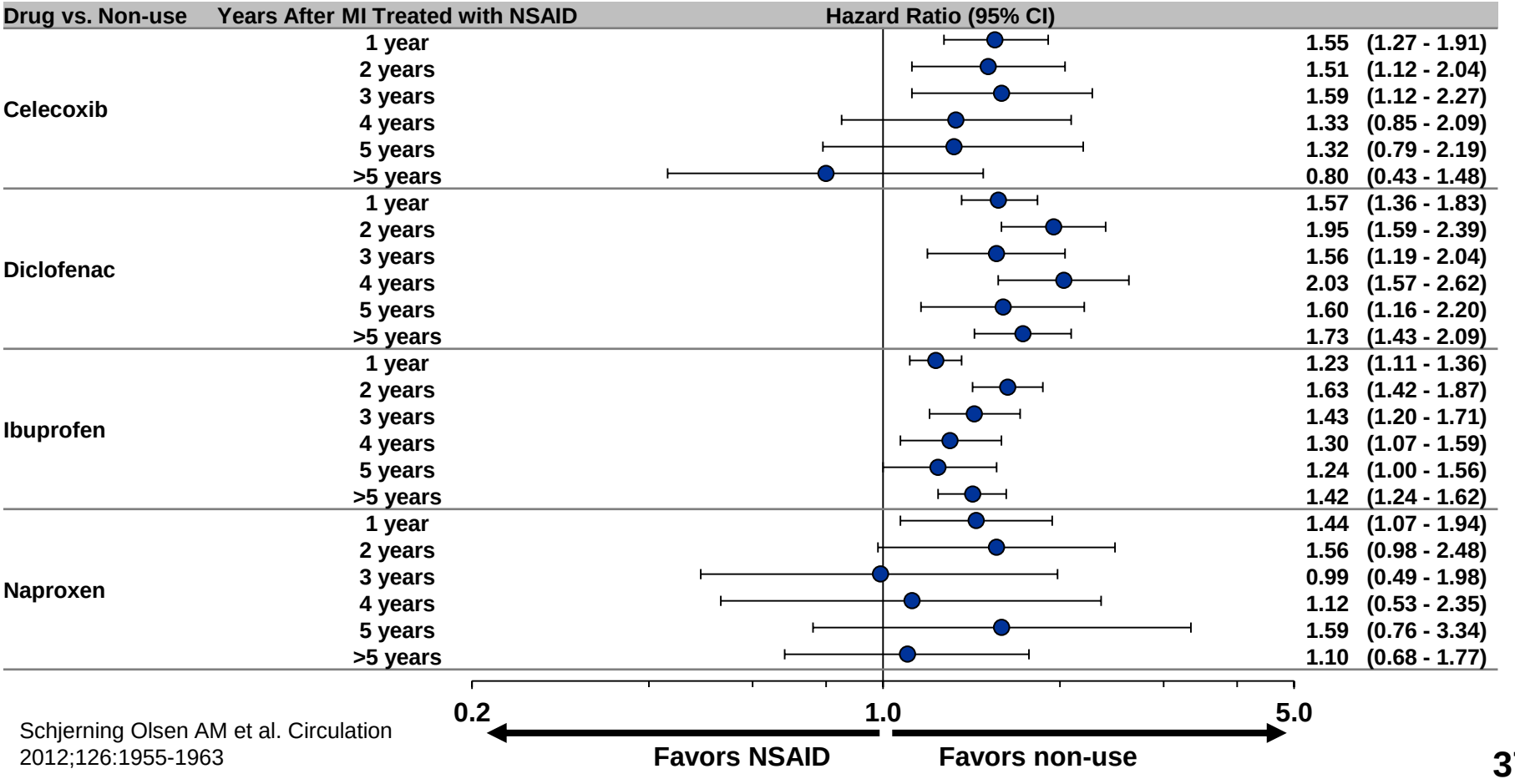
McGettigan and Henry Meta-Analysis of Observational Studies

Drug	Number of Studies			Risk Ratio (95% CI)	Relative Risk Ratio (95% CI)*
	Case-control	Cohort	Common to Naproxen and NSAID		
Naproxen	24	17	-	1.09 (1.02 - 1.16)	-
Ibuprofen	21	17	32	1.18 (1.11 - 1.25)	1.09 (1.03 - 1.15)
Celecoxib	20	15	23	1.17 (1.08 - 1.27)	1.04 (0.92 - 1.18)
Diclofenac	16	13	25	1.40 (1.27 - 1.55)	1.22 (1.13 - 1.32)
Rofecoxib	19	15	Not Given	1.45 (1.33 - 1.59)	Not Given

*The ratio of relative risks come from a direct comparison of studies common to naproxen and the specific NSAID
McGettigan P, Henry D PLoS Med 2011;8:e1001098

Coronary Death or MI Associated with NSAID Treatment After MI

Danish National Patient Registry, Schjerning Olsen et al. 2012



Schjerning Olsen AM et al. Circulation 2012;126:1955-1963

Coronary Death or MI Associated with NSAID Treatment After MI

Danish National Patient Registry, Schjerning Olsen et al. 2012

Drug	Hazard Ratio (95% CI) Combined Over All Six Time Intervals	
	vs. Non-use	vs. Naproxen
Naproxen	1.34 (1.10 - 1.63)	-
Celecoxib	1.46 (1.27 - 1.67)	1.09 (0.86 - 1.38)
Diclofenac	1.72 (1.57 - 1.87)	1.28 (1.03 - 1.59)
Ibuprofen	1.36 (1.29 - 1.45)	1.02 (0.83 - 1.25)
Rofecoxib	1.71 (1.50 - 1.95)	1.27 (1.01 - 1.62)

Schjerning Olsen AM et al. Circulation 2012;126:1955-1963

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Conclusions

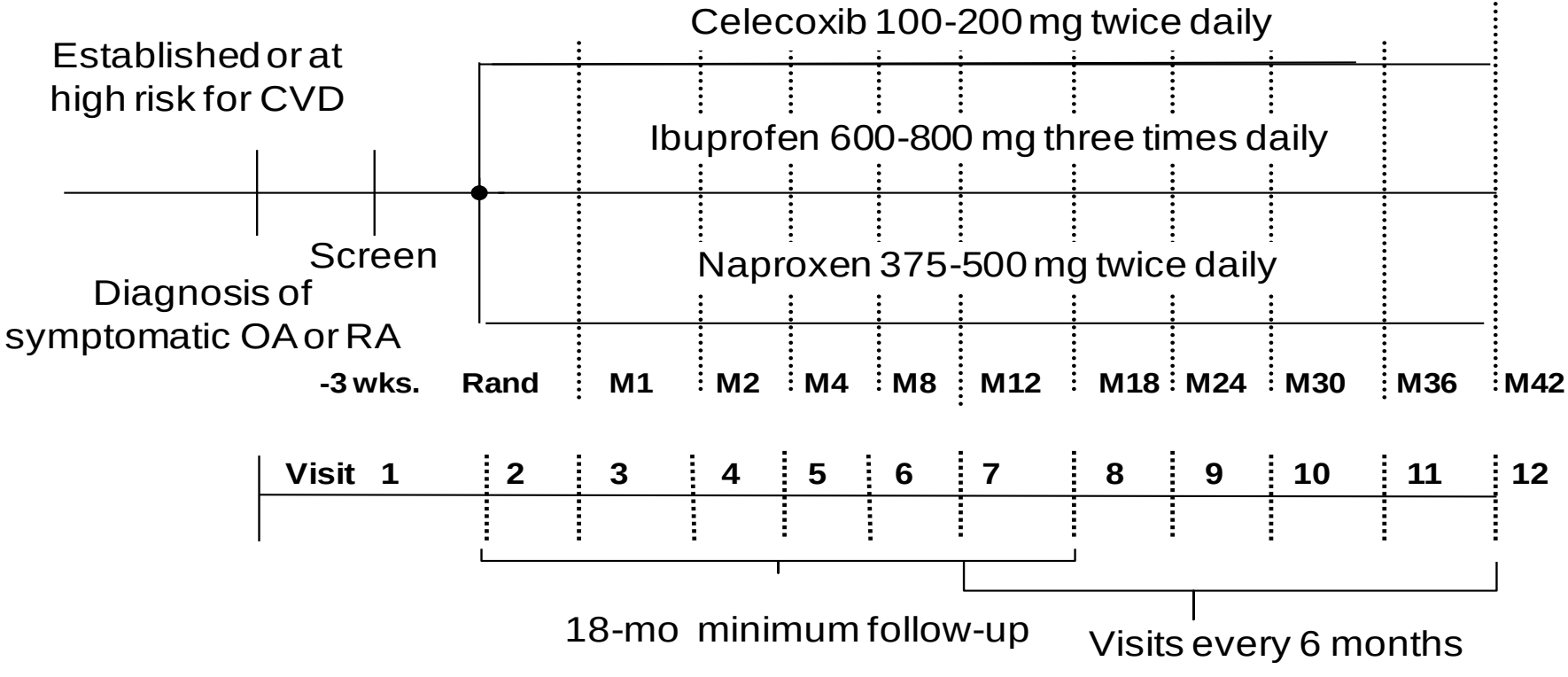
- The data show conflicting and inconclusive results on increased CV risk that do not support one NSAID being distinguished from the class effect
- Existing labeling reflects the known level of CV and other risks for NSAIDs. The data do not support differentiation for naproxen
- The data available since 2005 are not sufficient to change the existing class labeling concerning latency
- Current NSAID labeling warns about the risk for CV events in populations at higher risk for these events, and remains sufficient

Conclusions (continued)

- There is little evidence of an increased risk for CV events with nonprescription NSAIDs, including ibuprofen, at recommended doses and duration

- The evidence suggests that celecoxib, naproxen, and ibuprofen remain in equipoise. The decision to continue the PRECISION trial should remain with the Data Monitoring Committee. PRECISION will provide important information on 3 commonly used prescription NSAIDs

PRECISION Randomized Clinical Trial Design



CVD, cardiovascular disease
ClinicalTrials.gov Identifier: NCT00346216

PRECISION: Current Status

(Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen Or Naproxen)

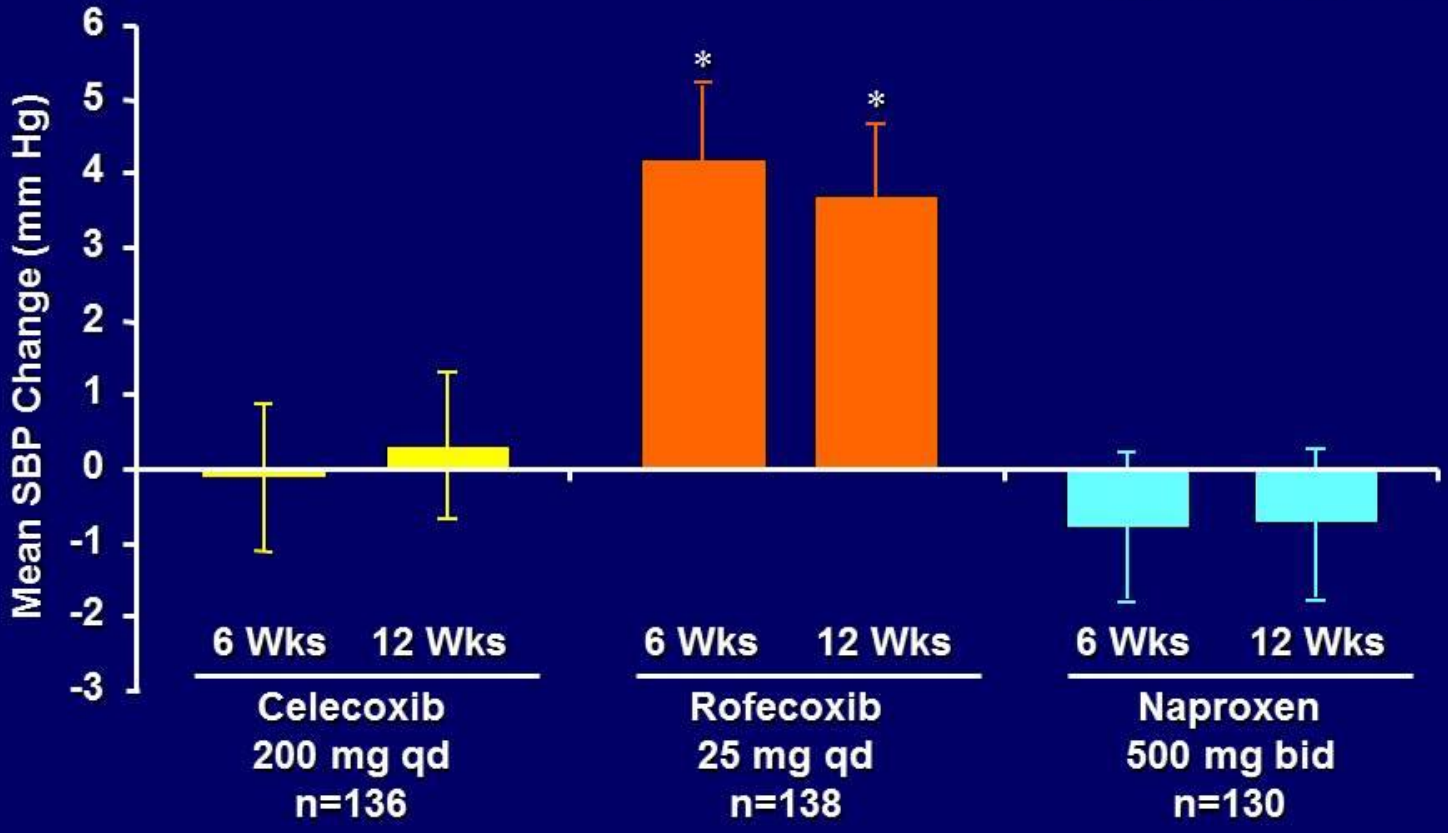
Steven E. Nissen, MD

Principal Investigator, PRECISION

Chairman, Cardiovascular Medicine, Cleveland Clinic

24-Hour Mean SBP Change at 6 &12 Wks in OA Hypertensive Patients

SBP from ABPM data



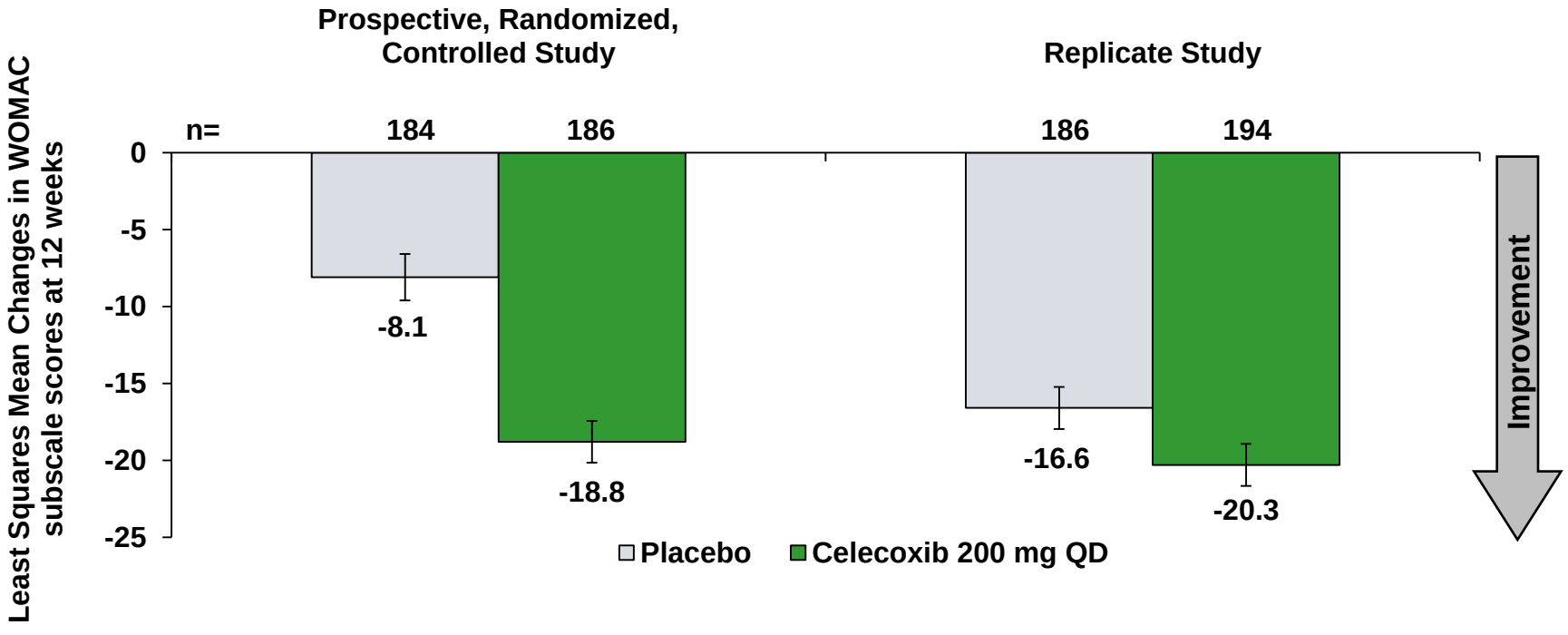
Sowers et al. Arch Int Med; 2005;165:161-168

* $p < 0.05$ vs other treatments

T14

Knee Osteoarthritis: Efficacy in Improving WOMAC Scores in Non-Responders

Celecoxib improved WOMAC Scores in subjects unresponsive to naproxen or ibuprofen*



*Subjects were nonresponsive to treatment with prescription-strength naproxen (≥750 mg/d for 2 weeks) and ibuprofen (≥1200 mg/d for 2 weeks) or had failed a trial of naproxen and ibuprofen of any duration if failure was due to lack of tolerability; QD, once daily

THE PRECISION TRIAL

THE PRECISION TRIAL

Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or Naproxen

Steven E. Nissen MD
Principal Investigator

THE PRECISION TRIAL

Cleveland Clinic Cardiovascular Coordinating Center

Protection of Trial Scientific Integrity

- By agreement between Sponsor, Data Monitoring Committee, and Executive Committee, this presentation about a trial that is still blinded will be limited to information appropriate for an ongoing study.
- We believe the PRECISION trial offers the best opportunity to answer a critically important clinical and scientific question.
- We do not want to compromise the scientific integrity of the study by releasing any data that might inappropriately influence study conduct.
- Your understanding is appreciated.

THE PRECISION TRIAL

The Key Issues

- **Patients with arthritis are often older and many have either concomitant heart disease or high risk features. Withholding pain relievers is not an option.**
- **The relative safety of celecoxib vs. non-selective NSAIDs unknown. Prior trials often studied *low-risk, non-arthritic* populations, used unapproved dosages, and had few CV events.**
- **Do all NSAIDs carry the same risks? There exist no placebo controlled CV trials with conventional NSAIDs.**
- **Only a large, prospective comparative trial in patients at *high CV risk* can resolve this question.**

THE PRECISION TRIAL

Scientific Governance

PRECISION is an academically-directed trial. Although funded by Pfizer, the scientific governance resides with an unpaid independent Executive Committee

- **Principal Investigator and Study Chair- Dr. Steven Nissen**
  - A. Michael Lincoff, MD - Associate Principal Investigator
- **Executive Committee**
- **Independent Data Safety Committee**
  - Chair - Dr. Thomas Fleming - University of Washington

THE PRECISION TRIAL

Multidisciplinary Leadership

- **Cardiologists**
  - Peter Libby, MD – BWH / Harvard
  - Thomas Luscher, MD – University of Zurich, Switzerland
  - Jeff Borer, MD – SUNY Downstate Health Sciences Center
  - Alice Mascette, MD – NHLBI (retired)
- **Rheumatologists**
  - M. Elaine Husni, MD, MPH – Cleveland Clinic
  - Daniel H. Solomon, MD, MPH – BWH / Harvard
- **Gastroenterologists**
  - David Graham, MD – Baylor / VAMC
  - Neville Yeomans, MD – University of Melbourne, Australia
- **Pfizer non-voting Representative**
  - Michael Gaffney, PhD – VP Statistical Research & Consulting

Data Monitoring Committee

- **Thomas R. Fleming, PhD, Chair – University of Washington**
- **Cardiology**
  - James (Jay) Brophy, MD, PhD – Royal Victoria Hospital, Quebec
- **Rheumatology**
  - Leslie J. Crofford, MD – Vanderbilt University, TN
- **Gastroenterology**
  - David Peura, MD – University of Virginia
- **Independent Statistical Services**
  - Axio Research – Seattle, WA

THE PRECISION TRIAL

Academic Independence

- By prior agreement, all academic members of the study leadership have agreed not to accept any consulting or other payments from makers of NSAIDs for the duration of the trial.
- All members of these committees file an annual disclosure. Any potentially relevant conflicts of interest are peer-reviewed by the Executive Committee.
- Copy of study database will be held by the Cleveland Clinic Coordinating Center for Clinical Research (C5R).
- My participation in today's meeting is not funded by Pfizer.

THE PRECISION TRIAL

Primary Objective

- To assess the effects of celecoxib 100-200mg bid and ibuprofen 600-800mg tid compared with naproxen 375-500mg bid on the first occurrence of the Anti-Platelet Trialists Collaboration (APTC) composite cardiovascular endpoint (CV death, non-fatal MI, non-fatal stroke)

Secondary Objectives

- To compare and evaluate incidence of:
  - Extended MACE - Composite of CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, revascularization, hospitalization for TIA
  - Clinically significant GI events (CSGIEs)
  - Effects on renal function and blood pressure
  - Arthritis efficacy: Pain, global improvement, function

Noninferiority Trial Design

- **Double Blind, Triple-Dummy, Multicenter, Parallel-Group Study of Cardiovascular Safety in OA or RA Patients with or at High Risk for Cardiovascular Disease Comparing Celecoxib with Naproxen and Ibuprofen**
- **Estimated 20,000 subjects randomized 1:1:1 to one of these three treatment options; stratified according to:**
  - Treatment center
  - OA vs. RA indication
  - Aspirin use
- **Anticipate 35% non-aspirin users (at randomization)**

THE PRECISION TRIAL

Adjudicated Endpoints

- APTC - Primary
  - CV death, non-fatal MI, non-fatal stroke
- Other clinically significant CV or renal events
  - Hospitalization for unstable angina, CHF, HTN, TIA
  - Revascularization – coronary, cerebrovascular, peripheral
  - Renal insufficiency/failure

THE PRECISION TRIAL

Adjudicated Endpoints

- Clinically significant GI events (CSGIES)
  - Gastric or duodenal hemorrhage
  - Gastric outlet obstruction
  - Gastro-duodenal or small-large bowel perforation
  - Large or small bowel hemorrhage
  - Acute GI hemorrhage of unknown origin
  - Symptomatic gastric or duodenal ulcer
- Clinically significant iron deficiency anemia of GI origin

Trial Design and Duration

- ITT analysis truncated at 30 months, per protocol at 42 months, 18 month minimum follow-up
- Visits: Screening, Baseline for Randomization. Months 1, 2, 4, 8, 12, then every 6 months, end-of-study, and 30-day phone follow up.
- Study completion after 762 primary endpoints and all subjects followed a minimum of 18 months
- Non-inferiority for both intention-to-treat (primary) and per protocol populations required.
- Estimated 1000 centers in approximately 16 countries

THE PRECISION TRIAL

Definition of Non-inferiority: 4 Components

Protocol amended to provide 80% power, which required fewer endpoints

	Point estimate	95% upper confidence interval
ITT Population (580 events)	<1.11	<1.33
Per protocol population (420 events)	<1.11	<1.4*

THE PRECISION TRIAL

*Amended from 1.33 after discussion with FDA

Study Performance Standards

Standards	Target Rate	Minimally Acceptable
Enrollment	500 / month	350 / month
Target Population (highest risk category)	≥ 40%	≥ 35%
Subject Ineligibility	≤ 5%	≤ 10%
Cross-ins	≤ 2.5%	≤ 10%
Withdrawal from Treatment	≤10% in first 3 months	≤15% in first 3 months
Study Drug Compliance 80 – 120%	≥ 80%	≥ 60%
Non-Retention	≤2%	≤5%

Key Inclusion Criteria

- **Males or females ≥ 18 years of age**
- **Duration of OA or RA ≥ 6 months**
- **Requirement for chronic analgesic regimen ≥ 6 months**
  - Stable doses of DMARDs or oral corticosteroids (≤ 20mg prednisone or equivalent daily)
  - Same medications for minimum of 3 months
    Same dosage regimen for minimum of 1 month
- ***Requires chronic, daily NSAID therapy to control arthritis symptoms***

Maintenance of Equipoise

- *Key provision:* Patients must have required an analgesic regimen continuously (>50% of time) for 6 months prior to enrollment in order to complete activities of daily living.

- *Rationale:* Justification for giving NSAIDs to a population at high cardiovascular risk requires evidence for a clear patient benefit to offset potential risks.

Key Inclusion Criteria

a) **Known coronary artery disease**

b) **Occlusive disease of non-coronary arteries**

c) **DM: Clinical diagnosis of type I or II. Female patients require current insulin treatment.**

d) **High risk of atherosclerotic vascular disease by multiple criteria. Females require at least two of the following three:**

- Age ≥ 65 yrs
- History of hypertension
- Current smoking (any cigarette within the past 30 days)

THE PRECISION TRIAL

Key Exclusion Criteria

- MI, stroke, unstable angina, CABG, or cardiac electrophysiologic instability within 3 months prior to randomization
- Uncontrolled hypertension or NYHA Class III or IV CHF or known EF ≤35%.
- Esophageal, gastric, pyloric channel or duodenal ulcer ≤ 60 days prior to randomization. History of GI perforation, obstruction or bleeding ≤ 6M prior to randomization

Trial Treatments

Dosing in accordance with approved labeling in respective participating countries

- **Celecoxib 100 – 200mg bid**
- **Ibuprofen 600 – 800mg tid**
- **Naproxen 375 – 500 mg bid**
- **Esomeprazole 20 – 40mg qd (open label)**

Start at lowest dose. May be increased or decreased based on subject symptoms per investigator discretion

Rationale for Choice of Comparators

- Celecoxib the only currently marketed Cox-2 selective NSAID
- Naproxen very widely used, non-selective NSAID, some analyses suggest less potential for thrombotic events.
- Ibuprofen also widely used, but intermediate in Cox-2 selectivity.
- Acetaminophen deemed not sufficiently effective to enable long term adherence, concerns about hepatotoxicity.
- Diclofenac not widely used in USA, deemed undesirable due to hepatic toxicity.

Concomitant Treatment

- Optimal preventive care for CV disease risk per local standards. May include aspirin, statins, ACE-inhibitors, beta-blockers, anti-platelet agents, and anti-hypertensive agents
- Aspirin
  - 75-100mg recommended
  - Administer two hours before study drug to reduce potential interaction that may decrease anti-platelet effects of aspirin

Rescue Analgesic Therapy

- Permitted for breakthrough pain
- Non-NSAIDs at discretion of investigator or primary care physician (within prescribing recommendations)
  - Acetaminophen
  - Opioids, tramadol, ~~propoxyphene~~, duloxetine
  - Intra-articular steroid or hyaluronic acid injection
- Non-pharmacologic treatments: physical therapy, TENS
- RA - May change DMARD, biologics, corticosteroid
- Continue study drug treatment
- Reassess within 2 weeks (unplanned visit)

Study Drug Interruption(s)

- Permitted at discretion of investigator to evaluate or treat subject for adverse event(s)
- Discontinue > 1 week then restart study drug
- Restart study drug therapy as soon as possible
- OTC or prescription NSAIDs or open label COX-2 selective NSAIDs are not allowed during the course of the study, including study drug interruptions

Headwinds

- EMEA declined to allow enrollment of patients stating that NSAIDs are unsafe in patients with cardiovascular disease.
- Observed event rates lower than anticipated.

Response:

- Statistical power reduced from 90% to 80%, thereby requiring fewer APTC events, 580 rather than 762.
- Enrollment restricted to highest cardiovascular risk category to increase event rates.
- Enrollment extended beyond the initial anticipated 20,000.

PRECISION: Unique Insights

- A “real-world” trial using three of the most commonly used pain relievers in the world.
- High risk CV patients studied for the first time.
- Full GI protection using a proton pump inhibitor.
- ASA permitted as indicated.
- More than 50,000 patient-years, substantially greater exposure than the CNT meta-analysis of all prior trials comparing celecoxib to ibuprofen or naproxen.
- All CV, GI, and renal endpoints prospectively adjudicated.

THE PRECISION TRIAL

Non-cardiovascular insights

- Evaluation of non-cardiovascular adverse events pivotal to obtaining a clear understanding of the risks and benefits of these alternative therapies.
- An ambulatory blood pressure substudy completed, but not yet unblinded.
- Comparative renal safety fully evaluated.
- Comparative GI safety fully evaluated.
- Comparative effects on symptomatology and QOL

Progress to Date (2/5/2014)

- DMC recommendation to enroll 23,750 patients
- Approximately 30,000 patients screened, 22,621 randomized (>95% of intended 23,750).
  Enrollment should complete during summer 2014.
- 486 sites following patients, 305 actively enrolling
- Requisite 18 months minimum follow-up results in final end-of-study visits approximately December 2015

THE PRECISION TRIAL

Comparison of Methodology: PRECISION Trial vs. CNT Meta-analysis

- **PRECISION directly and prospectively compares individual agents for multiple relevant endpoints (CV, GI etc.).**
- **Much of the information from CNT meta-analysis for comparisons between individual drugs derived indirectly:**
  - Drug A vs. placebo hazard ratio
  - Drug B vs. placebo hazard ratio
  - Drug A vs. Drug B derived indirectly
- **CNT meta-analysis groups all coxibs together. Most data for drugs no longer marketed (rofecoxib, lumiracoxib)**

THE PRECISION TRIAL

Ibuprofen Comparison: Number of Events in CNT Meta-Analysis vs. PRECISION Trial

Ibuprofen Comparison	Celecoxib events	Ibuprofen events	Follow-up (weeks)	RR (95% CI)
Celecoxib 800 mg	14	12	30	1.11 (0.38-3.30)
Celecoxib 400 mg	2	3	9	0.63 (0.04-9.45)
Celecoxib 200 mg	1	1	12	NA
Celecoxib all doses	17	16	-	1.01 (0.48-2.13)

PRECISION: Anticipating 193 events per dosage group (10x greater)

THE PRECISION TRIAL

Naproxen Comparison: Number of Events in CNT Meta-Analysis vs. PRECISION Trial

Naproxen Comparison	Celecoxib events	Naproxen events	Follow-up (weeks)	RR (95% CI)
Celecoxib 800 mg	0	1	9	NA
Celecoxib 400 mg	17	17	43	0.96 (0.38-2.48)
Celecoxib 200 mg	6	5	9	1.15 (0.20-6.52)
Celecoxib 100 mg	0	1	9	NA
Celecoxib all doses	23	17	-	0.93 (0.46-1.88)

PRECISION: Anticipating 193 events per dosage group (10x greater)

THE PRECISION TRIAL

Three Questions from Briefing Document about the PRECISION Trial

1. Is the trial still capable of meeting its objective because of specific study design features?

2. Is the trial still necessary to answer the research question?

3. Is the trial still considered reasonably safe for the participants?

THE PRECISION TRIAL

Issues Raised by Dr. Mosholder's Review of Precision

- The analysis will pool 200 mg/day and 400 mg/day dosages of celecoxib. There is now evidence that these dose levels convey different CV risks, but dose subgroup analyses are likely to be underpowered.

- Sixty-five percent* of the subjects are to be receiving low dose ASA for cardioprotection at baseline. The protocol states that subjects are to take ASA two hours before their study medication, to avoid interference with ASA's antiplatelet activity by ibuprofen and naproxen. If this advice is not followed, subjects receiving ibuprofen or naproxen will have a diminished level of cardioprotection, biasing the trial in favor of celecoxib, which does not interfere with ASA.

* Estimated in protocol

Issues Raised by Dr. Mosholder's Review of Precision

- Analyzing ASA users and nonusers in separate subgroups will be necessary to evaluate this potential interaction, but the trial is not statistically powered for these subgroups. In addition, data will be needed on whether subjects initiated or discontinued ASA during the trial, not just whether they were receiving ASA at randomization.

- To interpret data from the subgroup of ASA users properly, data will also be needed regarding how vigorously, and how successfully, those subjects were encouraged to take ASA two hours prior to their study medication.

Issues Raised by Dr. Mosholder's Review of Precision

- The ITT analysis is likely to be compromised by misclassification of exposures, to the extent that subjects discontinue treatment or switch drugs. The statistical power for the more easily interpreted modified-ITT analysis will be lower than for the main ITT analysis.

- In general, any factor that biases the trial towards a null result will support the sponsor's goal of declaring celecoxib non-inferior to the other treatment

Three Questions from Briefing Document about the Precision Trial

1. Is the trial still capable of meeting its objective because of specific study design features? Yes

2. Is the trial still necessary to answer the research question?

3. Is the trial still considered reasonably safe for the participants?

THE PRECISION TRIAL

PRECISION DMC (12/12/13 Meeting)
Importance of Next 18-24 Months

The Precision Trial will complete late next year. While it already is near full enrollment (>95%) and a substantial fraction of the targeted 580 events already have occurred, the DMC has confirmed that the remaining events to be captured during the next 18-24 months could have a very substantive impact on the interpretability and reliability of trial results.

THE PRECISION TRIAL

PRECISION DMC (2/6/14 Meeting)
Importance of Continuing as Designed

"While it awaits insights from Advisory Committee deliberations, the DMC has carefully reviewed the FDA briefing document. Based on insights from this document and > 40,000 patient years of follow-up currently available in PRECISION, the DMC has strongly concluded":

- **"PRECISION is still capable of meeting its objectives."**
- **"Its role is integral in addressing the research questions."**
- **"It is reasonably safe for participants."**
- **"It is important that PRECISION continue as designed."**

THE PRECISION TRIAL

Three Questions from Briefing Document about the Precision Trial

1. Is the trial still capable of meeting its objective because of specific study design features? Yes

2. Is the trial still necessary to answer the research question? Yes

3. Is the trial still considered reasonably safe for the participants? Yes

Implications of a Change in Labeling for Naproxen

- **Prematurely Re-labeling naproxen based upon observational data and/or CNT meta-analysis would have profound impact on our ability to complete the PRECISION Trial, which will provide far more reliable conclusions.**
- **Equipoise in the PRECISION trial depends on uncertainty about relative CV and GI safety of non-selective NSAIDs vs. celecoxib, which we believe *clearly* still exists.**
- **Re-consenting all patients based on limited and imprecise data would seriously undermine efforts to retain patients and reduce the likelihood of a reliable result.**

THE PRECISION TRIAL

Summary and Conclusions

- The CNT meta-analysis provides a summation of prior trials, but use of indirect comparisons, the limited number of events, short duration of follow-up, and inclusion of unapproved high dosages of medications no longer marketed warrant very cautious interpretation.
- Determining the relative safety of Cox-2 selective and non-selective NSAIDs is best accomplished through a large randomized trial conducted using the highest possible standards of trial conduct.
- The PRECISION trial is carefully designed to provide insights into both cardiovascular and non-cardiovascular safety.

THE PRECISION TRIAL

THE PRECISION TRIAL